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PAPER

3-Methoxalylchromones – versatile reagents for the regioselective synthesis of functionalized 2,4′-dihydroxybenzophenones, potential UV-filters†

Viktor O. Iaroshenko,*[a,b] Alina Bunescu,[a,c] Anke Spannenberg,[c] Linda Supe,[a] Maria Milyutina[a] and Peter Langer*[a,c]

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The reaction of 1,3-bis-silyl enol ethers with 3-methoxalylchromones affords a great variety of functionalised 2,4′-dihydroxybenzophenones. These products are formed by a domino Michael/retro-Michael/Mukaiyama-aldol reaction. The synthesized compounds are promising candidates for the synthesis of the novel UV-A/B and UV-B filters.

Introduction

Organisms rely on nucleic acids (RNA and DNA) for storage of their genetic information encoded in the sequences of the four nucleobases adenine, cytosine, guanine and thymine (uracil in RNA). The damage of the DNA and RNA matrix causes mistakes during the replication and transcription, which leads to mutations of the genome and disorders in cell functions. Ultraviolet radiation can cause damages of nucleic acids.[1,2] The most dangerous sunlight radiation lies in the range of < 280 nm, the so-called UV-C band, however, this UV light is absorbed by ozone in upper parts of the atmosphere.[2] The UV-B (320–290 nm) and UV-A (400–320 nm) bands remain in the sunlight and also contribute significantly to the negative effects of sun radiation.[1,2]

Overexposure to sunlight causes dimerization of two pyrimidine molecules (*e.g.*, [2 + 2] cycloaddition of thymine), which is the most important photoreaction caused by UV-B and UV-C radiation of DNA in cells. This results in photoallergic and cytotoxic reactions and skin cancer; the latter is induced by photochemical reactions of the DNA.

An important way to protect the skin against UV radiation relies on the application of sun-creams. Optimal sun-creams should have a broad and strong absorption of UV-A (400–320 nm) and UV-B radiation (320–280 nm).[3] Other important parameters of sun-creams include photostability, thermostability, chemical stability (particularly against water) and a moderate lipophilicity. Sun-creams often contain a mixture of UV-A and UV-B filters.[3] Salicylates (*e.g.* ethylhexyl salicylate) and dibenzoylmethanes (*e.g.* 4-butyl-4-methoxydibenzoylmethane) are widely used as UV-A filters. Alternatively, UV-A/B filters, which combine a UV-A and UV-B filter in one molecule, are also frequently employed. Functionalised benzophenones, such as benzophenone-3 (oxybenzone), are widely used in UV-A/B filters.[3] However, due to allergic reactions caused by the photosensitizing effects of oxybenzone, the development of new UV-A/B filters is of considerable interest.[3]

On the other hand, molecular composites containing benzophenones are widely used as photosensitizers. Due to the photochemical properties of the benzophenone scaffold, they represent one of the most important substance classes in photochemistry.[4] Functionalised 2-hydroxybenzophenones are widely used as sun-creams.[3] At the same time, functionalised benzophenones have found various medicinal and technical applications. They occur in a variety of natural products and represent important core structures for the development of pharmaceuticals.[5] For example, the benzophenone phenstatin has been reported to be an antitubulin agent.[6]

We have previously reported that 2,4′-dihydroxybenzophenones can be prepared by domino reaction of 3-acetyl- and 3-formylchromones **1a, b** with functionalised 1,3-bis-silyl enol ethers.[7] Recently, we have reported the synthesis of 3-methoxalylchromone,[8a] containing an additional ester group, and its reactions with electron-rich nitrogen heterocycles. Herein, we report what are, to the best of our knowledge, the first reactions of 3-methoxalylchromone and related derivatives with 1,3-bis-silyl enol ethers. These reactions result in the diastereoselective formation of highly functionalized 9-oxo-4,4a,9,9a-tetrahydro-1*H*-xanthenes instead of the expected benzophenones. However, the corresponding tetrahydro-1*H*-xanthenes could be transformed into functionalized benzophenones by treatment with *para*-toluenesulfonic acid. The products reported herein are not readily available by other methods.

Results and discussion

The synthesis of 3-methoxalylchromones **3a–c** and 3-(dichloroacetyl)chromone **4**, containing a $CHCl_2$ group as a

[a]*Institut für Chemie, Universität Rostock, Albert-Einstein-Str., 3a, 18059, Rostock, Germany. E-mail: viktor.iaroshenko@uni-rostock.de; Fax: +49 381 49864112; Tel: +49 381 4986410*
[b]*National Taras Shevchenko University, 62 Volodymyrska st., Kyiv-33, 01033, Ukraine. E-mail: iva108@googlemail.com*
[c]*Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str., 29a, 18059, Rostock, Germany*

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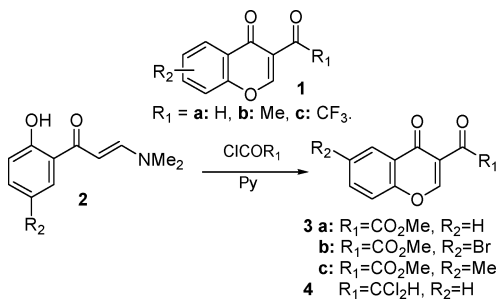
Table 1 Optimization of the synthesis of **6f**

3 : 5:TMSOTf	Activation Time	Reaction Temperature	%[a] **6f**
1 : 2 : 1	1 h	0 °C	16
1 : 2 : 2	1 h	0 °C	42
1 : 2 : 3	1 h	0 °C	38
1 : 4 : 2	1 h	0 °C	22
1 : 2 : 2	15 min	0 °C	0[b]
1 : 2 : 2	1 h	−78 °C	0[b]

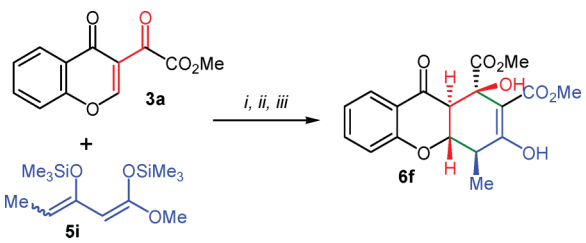
[a] Yields of isolated products. [b] No conversion (by TLC).

masked formyl group, and their reactions with amino-substituted heterocycles have recently been reported.[8] Based on our previously reported studies related to the reaction of 1,3-bis-silyl enol ethers (Table 1, ESI†) with 3-acetyl- and 3-formylchromones,[7] we expected that the reaction of **3a–c** and **4** with 1,3-bis-silyl enol ethers would result in the formation of 2,4′-dihydroxybenzophenones containing an additional ester group. As a test reaction, the reaction of **5i** with **3a** was carried out which surprisingly yielded 9-oxo-4,4a,9,9a-tetrahydro-1*H*-xanthene **6f** as the major product (Scheme 1). By optimization of the reaction conditions, we have found that the best yield was obtained using TMSOTf as the catalyst (Table 1). In contrast, the use of $TiCl_4$, $AlCl_3$, $AlBr_3$, $TiBr_4$, and $SnCl_4$ resulted in a failure (formation of mixtures of unidentified products). The stoichiometry and reaction time also played an important role.



Scheme 1 Formation of 3-methoxalylchromones **3** and 3-(dichloroacetyl)chromone **4**.

With the optimized reaction conditions in hand we have directed our efforts toward the study of the scope and limitation of the reaction. 1,3-Bis-silyl enol ethers **5**, readily reacted with **3a–c** to give the coresponding polycyclic products **6a–j** in 41–80% yields and with excellent diastereoselectivity (Schemes 2 + 3, Table 2). The variation of the substituents at the terminal position of **5** has

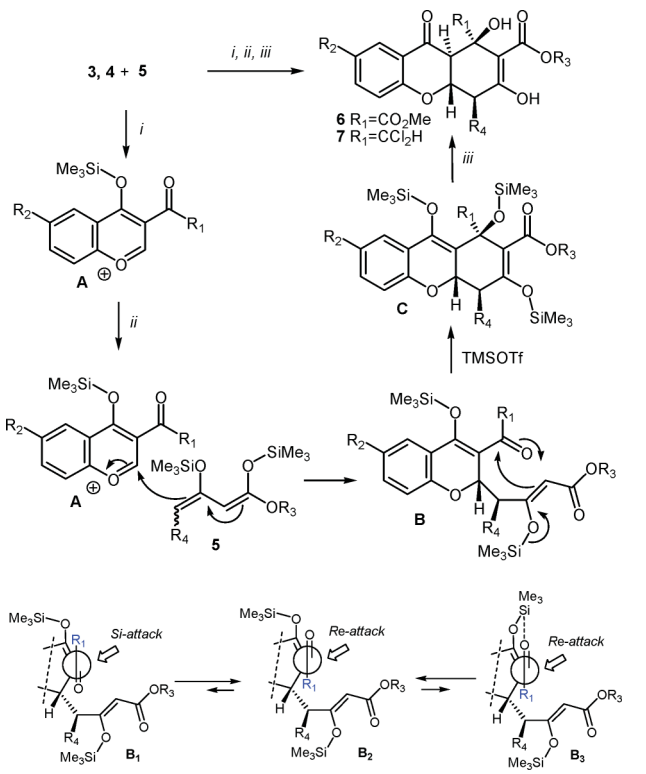


Scheme 2 *Reagents and conditions*: (i): **3a** with TMSOTf, 20 °C, 1 h; (ii): **5a–j**, CH_2Cl_2, 0–20 °C; (iii): 10% HCl.

Table 2 Synthesis of compounds **6** and **7**

6	**5**	R_1	R_2	R_3	R_4	%[a]
a	**a**	CO_2Me	H	Me	H	52
b	**b**	CO_2Me	H	Et	H	47[b]
c	**c**	CO_2Me	H	Bn	H	41[b]
d	**f**	CO_2Me	H	*i*-Bu	H	43[b]
e	**g**	CO_2Me	H	*i*-Pent	H	52[b]
f	**i**	CO_2Me	H	Me	Me	42
g	**a**	CO_2Me	Br	Me	H	51
h	**f**	CO_2Me	Br	*i*-Bu	H	80
i	**a**	CO_2Me	Me	Me	H	71
j	**d**	CO_2Me	Me	*i*-Pr	H	45
7[c]	**i**	CCl_2H	H	Me	Me	54

[a] Yields of isolated products. [b] These compounds were not transformed to **8**. [c] Compound **7** exist in a keto form (Fig. 3).



Scheme 3 Proposed mechanism. *Reagents and conditions*: (i): **3** or **4** with TMSOTf, 20 °C, 1 h; (ii): **5**, CH_2Cl_2, 0–20 °C; (iii): 10% HCl.

a influence on the yields. In addition, we have observed the highest yields for R_3 = *i*-Bu and R_2 = Br.

Having studied the reaction of chromones **3** with 1,3-bis-silyl enol ethers **5** we have switched on the chromone **4**. 3-Dichloroacetylchromone **4** was synthesised following the same strategy used for **3** (Scheme 1). The chemical behaviour of **4** in the reaction with **5** is not similar to **3**. It should be mentioned that starting with 1,3-bis-silyl enol ether **5i**, the product **7** was formed with a higher yield than **6f**. Product **7** was formed as a mixture of diastereomers, that makes the NMR methods not sufficient to corroborate the obtained structure. Following the same procedure with other 1,3-bis-silyl enol ethers **5** the reaction of **4** delivered a mixture of diastereomers, which could not be separated.

Recently, Sosnovskikh *et al.*[9] developed the synthesis of diverse 3-(polyfluoroacyl)chromones **1c**. We and others[10] studied the

application of these chromones for the preparation of many heterocycles and carbocycles. In this context we considered compounds **1c** as the suitable building blocks for the benzophenones synthesis (Fig. 1). Unfortunately, all reactions of **1c** with 1,3-bis-silyl enol ethers experienced a failure. The reason can be that chromones **1c** are existing in a form of the corresponding hydrate at the CF_3CO group.[9]

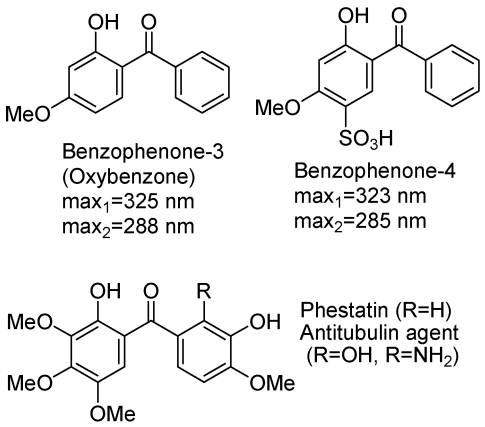


Fig. 1 Relevant benzophenone derivatives.

The mechanism of this interesting domino reaction is outlined in Scheme 3 and relies on three main steps. The initial formation of the O-TMS-pyrylium salt **A** is followed by attack of the (most nucleophilic) carbon atom C-4 of diene **5** on position 2 of the pyrylium salt to give adduct **B**. The subsequent TMSOTf-catalyzed intramolecular aldol condensation delivers intermediate **C**. The isolation of the products **6** and **7** was achieved after the addition of hydrochloric acid (10%), which resulted in cleavage of the TMS-groups (Fig. 2).

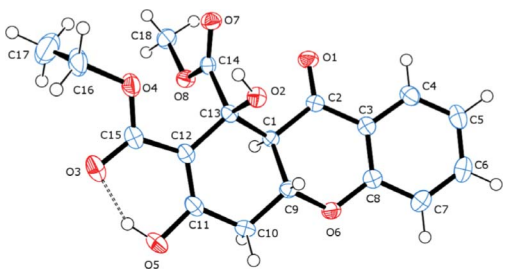


Fig. 2 Molecular structure of compound **6b**.

The structures of products **6** and **7** were established by spectroscopic methods. The structures of **6b**, **6c**, and **7** were independently confirmed by X-ray crystal structure analyses (Figs 2, 3 and 4 in ESI†).[11] The relative configuration of the products was assigned based on the crystallographic analysis. A *trans* relationship was observed for the bridgehead hydrogen atoms which is in good agreement with the coupling constant ($^3J_{H,H}$~ 13 Hz between these protons in the ^{1}H NMR spectrum). In the case of **7**, we have succeed to grow a single crystal, during the crystallization only one isomer precipitated, its structure was solved and is depicted on the Fig. 3.

This interesting phenomenon can be explained by the Felkin-Anh model throughout the mechanistic reaction presentation (Scheme 3). After the formation of the intermediate **B**, there are

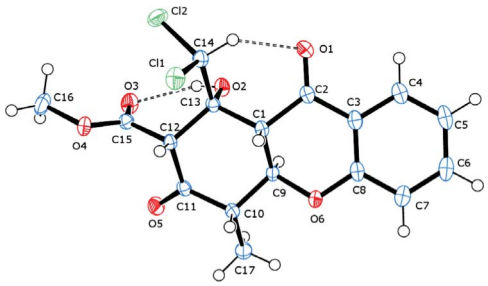


Fig. 3 Molecular structure of compound **7**.

two possible paths for the subsequent cyclohexene ring formation, namely *Re* and *Si* attack on the pro-chiral carbonyl group, each of it will deliver different diastereomers. Felkin–Anh model reveals that conformation $\mathbf{B_2}$ with lower energy should be predominant. On the other hand another driving force that stabilizes the conformation $\mathbf{B_2}$ is formation of the chelated moiety $\mathbf{B_3}$, where the carbonyl group is coordinated on the silica atom. Due to the facts mentioned above the *Re* attack is realizing for this cyclization delivering the only one diastereomer isolated.

The compounds from scaffold **6** exist in enol-form which is supported by the intramolecular hydrogen bond (Fig. 2). In contrary, in the case of compound **7**, where such bonding is not possible, the keto-form predominates (Fig. 3).

To perform the ring-opening reaction of **6**, acidic media were taken as reaction conditions. The substrate **6a**, which was taken as a model compound for the optimization of the reaction condition, underwent the desired ring-open cascade chemistry by the prolonged reflux in TFA to yield 2,4′-dihydroxybenzophenone **8a** as a single regioisomer, albeit in a disappointing yield of 22%.

A poor yield (20%) was obtained when the reaction was carried out in glacial acetic acid (reflux). During the optimization of the reaction conditions it was found that the best yield (63%) was obtained when *p*-toluenesulfonic acid (PTSA) in ethanol was employed. Moreover, it was applied a two-step one pot procedure starting from **3** and **5** to reach **8**; the yields in this case were significantly higher (Table 3).

The synthesis of **8j** took place in only one step, without PTSA/ethanol reflux, and the product precipitated with no need of further purification. This could also be observed in the case of **8k**. Unfortunately the aromatization in one step took place with only 32% yield so that the second step was needed to get 56% yield. The implicated reaction proceeds most probably *via* the formation of intermediates type **D**, **E**, depicted on the Scheme 4, that describes the presumable mechanism of the reaction.

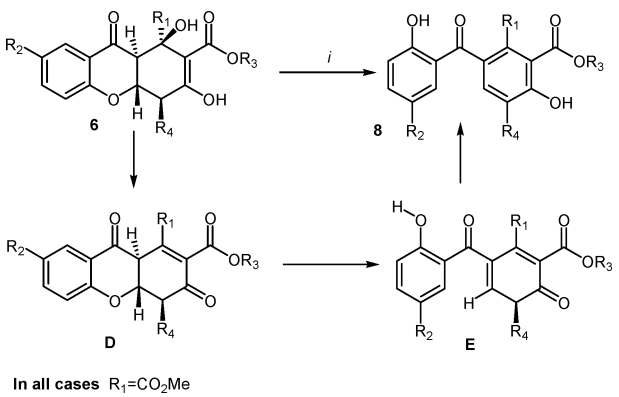
The ring-opening reaction, followed by aromatization did not take place for the derivative **7** containing CCl_2H-function. Both acidic media (PTSA/ethanol) and basic media (KOH/methanol) have been tried without success. A mixture of unidentified products was formed.

The constitution of scaffold **8** was established by crystallographic analysis of the obtained single crystals of compounds **8i** (Fig. 4), and **8j**, **8p** (Figures 5 and 6 in the ESI†).[11] The crystal structure of compound **8i** contains two intramolecular hydrogen bonds between O(1) and O(2), O(5) and O(7). The plane of the *ortho*-salicylic substituent is rotated about 57° regarding the central benzoic ring, the corresponding dihedral angle C(6)C(7)–C(8)C(13) is 70.3(2)°. In addition, the methoxycarbonyl group is

Table 3 Synthesis of benzophenones **8**

8	5[e]	R_2	R_3	R_4	%[a]
a	**a**	H	Me	H	63[b] (50[c])
b	**e**	H	*n*-Bu	H	84[b]
c	**h**	H	*n*-Oct	H	80[b]
d	**i**	H	Me	Me	67[b] (45[c])
e	**j**	H	Me	Et	66[b]
f	**k**	H	Me	*n*-Non	70[b]
g	**l**	H	Me	*n*-Tetradec	74[b]
h	**m**	H	Me	*n*-Hexadec	72[b]
i	**n**	H	Me	$(CH_2)_2Ph$	37[b]
j	**o**	H	Me	$(CH_2)_3Cl$	53[d]
k	**p**	H	Me	$(CH_2)_4Cl$	56[b] (32[d])
l	**a**	Br	Me	H	49[b] (45[c])
m	**f**	Br	*i*-Bu	H	72[b] (63[c])
n	**i**	Br	Me	Me	75[b]
o	**k**	Br	Me	*n*-Non	77[b]
p	**m**	Br	Me	*n*-Hexadec	54[b]
q	**p**	Br	Me	$(CH_2)_4Cl$	82[b]
r	**a**	Me	Me	H	60[b] (58[c])
s	**d**	Me	*i*-Pr	H	63[b]
t	**i**	Me	Me	Me	74[b]
v	**k**	Me	Me	*n*-Non	63[b]
w	**m**	Me	Me	*n*-Hexadec	72[b]

[a] Yields of isolated products. [b] Two step one pot procedure. [c] he reaction was conducted sequentially *via* the isolation of **6**. [d] Product isolated after the first step. [e] For list of **5** see Table 1 in the ESI.†



Scheme 4 *Reagents and conditions*: (i): EtOH, *p*-TsOH (3 mol%), reflux, 5–10 h.

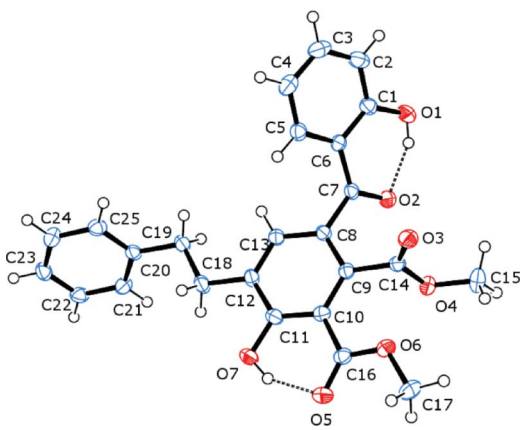


Fig. 4 Molecular structure of compound **8i**.

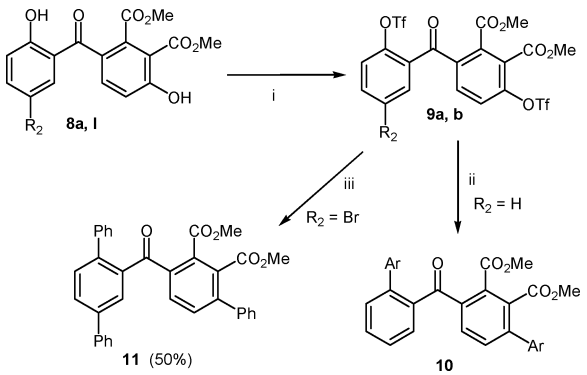
also not in the plane with the ring, the corresponding C(8)C(9)–C(14)O(3) angle is 57.4(2)°.

Table 4 Synthesis of benzophenones **10**

10	Ar	%[a]
10a	$(4\text{-}OCH_3)C_6H_4$	60
10b	$(4\text{-}C_2H_5)C_6H_4$	60
10c	$(4\text{-}Cl)C_6H_4$	70
10d	$(3\text{-}CF_3)C_6H_4$	39

[a] Yields of isolated products.

In order to modify the scaffolds **8** the Pd-mediated C–C couplings by the transformation of **8** into bistriflate derivatives with the subsequent application of Suzuki protocol was undertaken. As a model compound we have taken **8a**, which was successfully transformed into bistriflate derivative **9a** (Scheme 5). The Suzuki reaction of **9a** with arylboronic acids afforded the novel benzophenones derivatives **10a–d** in good yields (Scheme 5, Table 4). The reactions were carried out using $Pd(PPh_3)_4$ (6 mol%) as a catalyst. The employment of other bases, such as Cs_2CO_3, resulted in a decreased overall yield. Potassium phosphate (K_3PO_4) was used as the base and 1,4-dioxane (110 °C, 4 h) as the solvent. All products were isolated in pure form by chromatographic purification. In most cases, a small amount of the corresponding biphenyls could be detected in the crude product before chromatography (by ^1H NMR and GC-MS).



Scheme 5 *Reagents and conditions*: (i): CH_2Cl_2, pyridine (4.0 equiv) –78–0 °C, under argon atmosphere, 4 h; (ii): 1,4-dioxane Ar-$B(OH)_2$ (2.5 equiv), K_3PO_4 (3.0 equiv), 6 mol% $Pd(PPh_3)_4$, 90 °C, under argon atmosphere, 4 h; (iii): 1,4-dioxane, Ph-$B(OH)_2$ (4.0 equiv), KF (4.5 equiv), 7 mol% $Pd(PPh_3)_4$, 90 °C, under argon atmosphere, 4 h.

Similarly, compound **8l** (R_2 = Br) was successfully transformed into the bistriflate derivative **9b** and subsequently coupled with phenyl boronic acid. In this case, our optimal condition used for the synthesis of **10** experienced a failure, by delivering an inseparable mixture of bis-substituted products. By using KF instead of K_3PO_4 the synthesis of **11** was succeed with a yield of 50%.

UV-Study

To develop a new UV-A/B filter, the UV absorptions of the polycyclic system **6** and of the benzophenones **8** and **10** were studied (Tables 2–4 and Figs 1–3 in the ESI†).

Electron transfers ($\pi \rightarrow \pi^*$ resp. $n \rightarrow \pi^*$) in the benzophenones **8** resulted in three λ_{max} at 230 nm (UVC), 240–280 nm (UVC) and 315–380 nm (UVA/UVB). As expected, the best absorptions

were observed for high conjugated systems like benzophenones **10a–d** and **11**, with absorption coefficients ε = 25000–37000 $cm^{-1}mol^{-1}l$, which are very high compered with other known UVA/UVB filters.[3] These compounds exhibit strong absorptions in the range of λ_{max} = 230 nm (UVC) and 300 nm (UVB). Weaker absorptions coefficients were observed for the polycyclic system **6** at wavelengths similar to the ones of benzopenones **8**. This makes them to a less promising UVA/UVB filter.

For the absorption maxima of compounds **8** and **10**, electron-donor groups led to a slight blue shift, while electron-acceptor groups (Br, Cl, CF_3) led to a slight red shift.

Conclusion

In summary, a new two-step synthetic strategy for the assembling of new benzophenones derivatives by the domino-cascade reaction of 3-acylated benzo-γ-pyrones and 1,3-bis-silyl enol ethers was developed. This method gives a green light to a set of functionalized benzophenones which are of considerable interest as novel UV filters with good UV absorbing properties. Functionalization of the scaffolds was explored by Suzuki coupling reaction.

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11 Crystallographic data (excluding structure factors) for the structure **6b**, **6c**, **7**, **8i**, **8j**, and **8p** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 832478–832483 can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk, or *via* www.ccdc.cam.ac.uk/data_request/cif.

